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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/376,317	08/18/99	STOKES K	P-3569CON

EXAMINER	
BECKERLEG,A	
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DATE MAILED: 02/02/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/376,317	STOKES ET AL.	
	Examiner	Art Unit	
	Anne M Beckerleg	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-25,39-54 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-25,39-54 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Applicant's amendment and response received on 11/6/00 has been entered. Claims 55-60 have been canceled. New claim 61 has been added. Claims 5, 10, and 16 have been amended. Claims 1, 4-25, 39-54, and 61 are pending and active in the instant application. An action on the merits follows.

The text of those sections of Title 35 , US code, not included in this office action may be found in the previous office action, paper no. 2.

Claim Rejections - 35 USC § 112

The rejection of claims 56-60 under 35 U.S.C. 112, first paragraph, for lack of enablement is withdrawn in view of applicant's cancellation of the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-25, 39-54, and 61 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification discloses methods of delivering conduction protein genetic material to cardiac tissue comprising a delivery method which comprises a catheter, means for delivering said genetic material from a reservoir, mapping electrode means, and conductor means. The specification further discloses that the genetic material comprises nucleic acid vectors encoding a conduction protein such as a cardiac gap junction proteins. The specification on page 5 clearly discloses that the intended use for said delivery methods is for the treatment and/or correction of disturbances in the cardiac conduction pathway. It is also noted that claims 10-11 and 20-23 recite that a "therapeutically" effective amount of protein is delivered to the cardiac tissues. The specification does not provide an enabling disclosure for the delivery of therapeutically effective amounts of any conduction protein to cardiac tissues using any genetic material including nucleic acid vectors such that any effect on cardiac conduction is observed.

The specification does not provide sufficient guidance for genetic material encoding any conduction protein that can have any therapeutic effect on cardiac conduction when delivered using the instant methods. The specification provides prophetic exemplifications for the isolation and purification of nucleic acid molecules encoding the connexin proteins and insertion of connexin cDNA into plasmid and adenoviral vectors. The specification also provides general guidelines on recombinant DNA production including lists of potential promoters and

polyadenylation signals, and incorporates by reference the coding sequences for the connexins Cx40, Cx43, and Cx45. The specification fails to provide any guidance as to the identify, sequence, or biological properties of any conduction proteins other than the connexin family members listed above. Further, the specification fails to provide any guidance as to characteristics of genetic material encoding any conduction protein for use in the instant delivery system other than nucleic acid vectors. In regards to the use of vectors such as viral or adenoviral vectors disclosed by the specification, the specification fails to provide essential teachings on the method of delivery genetic material from said catheter delivery device such that any electrical energy generated by the device would not adversely impact the ability of the vectors to transduce cells in the cardiac tissue or damage the vector's stability and ability to express the encoded transgene. The specification does not disclose to what extent the administration of an electric field from the applicant's device will effect the quantity, structural integrity, and biological properties of DNA or RNA delivered into the cells as a result of any increase in the permeation of the cell membrane. It is well known in the art that the administration of an electric field, such as in the use of electroporation, can result in a significant level (e.g. 40-80%) of cell lysis (e.g. See Weaver et al., US Patent 5,019,034, column 3, lines 44-64). The specification also fails to disclose the manner and ability of any genetic material to transduce cardiac tissue cells which have been damaged due to the use of a helical electrode which is screwed into the myocardium.

In addition to the lack of guidance concerning the identity of conduction proteins for use in the instant invention other than connexins, the identity of genetic material other than nucleic

acid vectors, the effects of the claimed catheter delivery device on the ability of the cardiac tissue to take up foreign genetic material and the effects of the device on the ability of the genetic material to express any encoded protein as noted above, the specification fails to provide guidance as to the level of cardiac cell transformation, the types of cardiac cells transformed, and the level of expression of any conduction protein from any delivered genetic material that correlates with any effect on conduction in cardiac tissue *in vitro* or *in vivo*. The specification's sole disclosure of conduction proteins are members of the connexin family. At the time of filing, Kanter et al. discloses that the three members of the connexin gap junction family, Cx40, Cx43, and Cx45, have different biophysical properties, and that in combination they are believed to be important in the regulation of cellular coupling . Further, these proteins have regional differences in expression with the various cardiac tissues, such as the Purkinje fibers and ventricular myocytes, and they are not expressed in one-to-one-to-one ratios with any cardiac tissue (Kanter et la., page 861, column1-2, and page 866). The specification does not provide sufficient guidance that the expression of any level of any one connexin family member in any type of cardiac cell would have any effect on cardiac conductance. In view of the different biological properties of the connexin family members, the complex interactions between the family members that results in gap formation and cellular coupling, and the differential cellular distribution of the connexin family members, the skilled artisan would not have been able to predict whether the introduction of any connexin family member into any cardiac cell would result in any effect on cardiac conduction.

Furthermore, at the time of filing, the art did not consider the delivery and expression of therapeutic genes using nucleic acid expressions systems including viral vectors to be predictable. Verma et al. teaches that," ... the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable challenges" in gene therapy, and specifically identifies the "Achilles heel" of gene therapy as gene delivery (Verma et al. (1997) Nature, Vol. 389, page 239, column 1, paragraph 1, and column 3, paragraph 2).Verma points out that, " [t]here are considerable immunological problems to be overcome before adenoviral vectors can be used to deliver genes and produce sustained expression", that, " [a] critical limitation of retroviral vectors is their inability to infect non-dividing cells, such as those that make up muscle, brain, lung, and liver tissue " (Verma et al. (1997) Nature, Vol. 389, page 240, column 1, paragraph 3, and page 241, column 2, paragraph 2). Verma also teaches that the choice of an appropriate enhancer-promoter combination is critical to the level and consistency of gene expression from a particular vector and that , " .. the search for such combinations is a case of trial and error for a given type of cell" (Verma et al. (1997) Nature, Vol. 389, page 240, column 2, paragraph 2, and column 3, line 1). Marshall et al. concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall et al. (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1). Orkin et al. further states, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been

experimentally validated", that, "[m]ajor difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host", and that "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol.." (Orkin et al. (1995) Report to the NIH, page 1, paragraphs 3-4, and page 8, paragraph 2,). Thus, due to the art recognized unpredictability of achieving therapeutic levels of gene expression using nucleic acid vectors, the breadth of the claims, and the lack of guidance provided by the specification for the parameters affecting gene delivery and expression using the instant catheter delivery device, it would have required undue experimentation to practice the invention as claimed and the skilled artisan would not have predicted success in treating cardiac conduction disturbances by administering any genetic material encoding any conduction protein to cardiac tissue using the instant delivery methodology.

Claims 1, 4-15, 17-18, 20-25, 39-43, 45-46, 48-51, 53-54, and 61 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification discloses a catheter delivery device for delivering genetic material encoding a conduction protein to cardiac tissue. The specification does not provide adequate written description for genetic material encoding a conduction protein capable of affecting cardiac

conduction other than nucleic acid vectors encoding a connexin family member. The specification does not identify or describe the physical or biological properties of any type of genetic material encoding a protein which can affect conduction in cardiac tissue other than connexins Cx40, Cx43, and Cx45 and their incorporation in a vector such as a viral vector.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). With the exception of the genes referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides which may be capable of affecting conductance in cardiac tissue, or envision the detailed chemical structure of the encompassed polynucleotides which may be capable of expressing therapeutic levels of the encoded protein in any type of cardiac cell. As such, conception of the invention can not be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention. The nucleic acid itself is required. See *Fiers v. Revel,* 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Thus, the specification only meets the written description provision of 35 U.S.C. 112, first paragraph, for a conduction protein which is a connexin. Applicant is reminded that *Vas-Cath*

makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

The rejection of claim 5 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendment to claim 5.

The rejection of claim 10 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendment to claim 10.

The rejection of claims 17-19 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendment to claim 17.

The rejection of claim 25 under 35 U.S.C. 112, second paragraph, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection of the claims for reasons or record as discussed in detail below.

The applicant argues that the term peelable has a natural and adjectival meaning from to peel as "to strip off an outer layer or to remove by stripping". This definition does not clarify the term "peelable introducer sheath". The introducer sheath disclosed in the specification is a rigid metal device. It is unclear what portion of the sheath is removable by "stripping", or whether the

applicant intends that the entire sheath be removable. If the latter option is intended, it is suggested that the claims be amended to recite a " removable introducer sheath".

Claim Rejections - 35 USC § 103

The rejection of claims 1, 4-25, and 39-55 under 35 U.S.C. 103, over Mulier et al. in view of Leiden et al. and Kanter et al. is maintained over original, amended, or new claims 1, 4-9, 12-19, 24-25, 39-47, and 61. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds for rejection for reasons of record as discussed in detail below.

The applicant argues that Mulier teaches away from using the "ablation catheter" to deliver genetic material to cardiac tissue as the ablation catheter destroys the surrounding tissue and as such would not be expected to help restore conductive cell function in the cardiac tissue. The applicant's delivery system as claimed does not recite the limitation that the delivered genetic material has any effect on the cardiac tissue. The claims simply recite the delivery of genetic material to cardiac tissue. The intended use of the delivery method disclosed in the specification as the treatment of conduction disturbances does not have patentable weight for the purposes of prior art. As discussed in detail in the previous office action, the combination of references cited provides motivation for using the catheter system taught by Muelier to deliver genetic material to

cardiac tissue as taught by Leiden. Further, the skilled artisan would not consider the presence of tissue damage near the site of administration of genetic material as an obstacle to the transfection of nearby living cells. Therefore, as the limitation that the delivered genetic material must have a therapeutic effect on cardiac conduction is not recited by the instant claims, the applicant's arguments are not found persuasive and the rejection is therefore maintained.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Karen Hauda, can be reached at (703) 305-6608. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

Dr. A.M.S. Beckerleg